Curr Allergy Asthma Rep
DOI 10.1007/s11882-011-0198-3

Update on the Diagnosis and Treatment of Shellfish Allergy

Rosalía Ayuso

Abstract Shellfish allergy is a frequent, long-lasting, life-threatening disorder. As shellfish consumption increases, the number of allergic reactions to shellfish is expected to continue to rise as well. During the past decade, much has been learned about the allergens involved in shellfish allergy. Potential cross-reacting allergens between shellfish and other arthropods have been identified. As our knowledge of shellfish allergen improves, we will be able to develop more accurate methods of diagnosing shellfish allergy. In addition, extensive research is currently under way for the development of safer, more effective methods of managing shellfish hypersensitivity.

Keywords Shellfish · Crustaceans · Mollusks · Shrimp · Allergy · Allergens · Cross-reactivity · Diagnosis · Treatment · Anaphylaxis · Review

Introduction

Shellfish allergy is a long-lasting disorder usually persisting throughout life that is often associated with severe reactions, including life-threatening anaphylaxis. Allergenic shellfish comprise two major phyla: arthropods and mollusks. The phylum Arthropod contains the class Crustacea, which includes shrimp, prawn, crab, lobster, and crawfish. The phylum Mollusca includes the class gastropods (limpet, snail, abalone), bivalves (clam, oyster, scallop, mussel), and cephalopods (squid, octopus). A large variety of crustaceans are used for human consumption. Shellfish most frequently reported in allergic reactions are shrimp, crab, and lobster, followed by clam, oyster, and mussel [1]. Squid also has been reported as one of the shellfish that most frequently induces allergic reactions, second only to shrimp [2].

The black tiger shrimp *(Penaeus monodon)* (Pm) is the most widely cultured prawn species in the world, although it is gradually losing ground to the white leg Pacific shrimp (*Litopenaeus vannamei),* another prawn. More than 900,000 t are consumed annually. The brown shrimp (*Penaeus aztecus*) is a highly valued commercial fishery species, especially in the United States. Most of the studies on shellfish allergens have been conducted using these shrimp species. As shellfish consumption increases, the number of allergic reactions is expected to continue to rise as well. Therefore, it is important that accurate diagnostic methods and improved therapeutic options are developed for individuals with shellfish allergy.

Prevalence of Shellfish Allergy

As with other food allergies, accurate data on the prevalence of shellfish allergy are limited by the lack of controlled, population-based studies incorporating the gold standard of double-blind, placebo-controlled oral food challenge (DBPCFC). Shellfish rank among the seven main allergenic foods in children. Among adults, the most common allergenic foods are crustacean shellfish, fruits, peanuts, and tree nuts.

In general, the prevalence of immediate-type shellfish allergy is higher in areas with high shellfish intake. Recent studies from Canada and Asia using questionnaires found that

R. Ayuso (✉)
Department of Medicine and Pediatrics,
Division of Allergy and Immunology,
Mount Sinai School of Medicine,
One Gustave L. Levy Place, ANBG 17–80, Box 1198, New York, NY 10029, USA
e-mail: rosalia.ayuso@mssm.edu

Published online: 15 April 2011

shellfish allergy was reported in 0.5% of children in Canada, and 4% in Singapore and the Philippines [3, 4]. Among Spanish children, crustaceans and mollusks cause 3.8% and 1.6%, respectively, of food-induced allergic reactions and up to 33% of the food allergies in adults [2]. In the United States, a recent questionnaire-based survey by Sicherer et al. [1] found that 1 in 50 Americans claimed to be shellfish allergic. Rates of shellfish allergy were significantly lower for children than for adults (0.5% vs 2.5%), and lower in men than in women (1.5% vs 2.6%). The self-reported prevalence of mollusk allergy in this study population was 0.4% [1]. In another epidemiologic study, Liu et al. [5] found that the estimated prevalence of clinical shrimp allergy varied by age but was 1% overall. Shrimp sensitization, which was not measured in children younger than 5 years of age, did not vary appreciably by age and was the most frequent allergenic food in individuals older than 20 years of age. In addition, shellfish are also one of the most frequent foods causing emergency department visits in adults for food allergy and a significant number in children 6 years of age and older [6, 7]. However, shellfish-allergic patients seem to be less likely to be admitted to the hospital as a result of reactions to shellfish [8].

Identified Shellfish Allergens and Their IgE Epitopes

Shrimp species have been the most studied in terms of allergen characterization, particularly the black tiger shrimp (Pm) and the white leg pacific shrimp (*L. vannamei*). The muscle protein tropomyosin was the first major cross-reactive allergen identified in shrimp [9] and was named Pen a 1, Pen m 1, Lit v 1, or Met e 1, depending on the species in which it was identified. Pen a 1 inhibited 85% of patients' IgE radioallergosorbent test reactivity to whole body shrimp extract, indicating that it is responsible for most of the allergenic activity of shrimp. Proteomic analysis of Pm has resulted in the identification of a novel allergen, arginine kinase (AK), or Pen m 2 [10]. Recently, two new shrimp allergens have been characterized by our group: myosin light chain (MLC) (Lit v 3) [11] and a sarcoplasmic calcium-binding protein (SCP) (Lit v 4) [12]. Both allergens were found to be significantly important in pediatric populations. Although tropomyosin is the most abundant allergen in crustaceans, some of our study participants primarily recognized SCP. ELISA (enzyme-linked immunosorbent assay) inhibition experiments showed that a significant proportion of some individuals' shrimp-specific IgE (up to 78%) is inhibited by recombinant SCP, demonstrating that for some, SCP may be more important than tropomyosin as a shellfish allergen. Furthermore, the functional rat basophil leukemia (RBL)-based mediator release assay confirmed that for a subset of individuals, SCP appears to be a more potent basophil activator than tropomyosin [12]. With regard to other crustaceans, such as crab and lobster, tropomyosin has been identified as the main allergen. More recently, several additional allergens have been identified by our group. Lobster and crab troponin C, as well as shrimp hemocyanin were described as crustacean allergens that may be implicated in the cross-reactivity among arthropods (American Academy of Allergy Asthma and Immunology 2011).

To date, only one study has analyzed the frequency of reactivity of shrimp-allergic patients to peptides from the four main shrimp allergens (tropomyosin, MLC, SCP, and AK) using nonchallenged patients [13•]. The highest reactivity was found to tropomyosin (81%; 94% in children and 61% in adults), followed by MLC (57%; 70% and 31%, respectively), AK (51%; 67% and 21%, respectively), and SCP (45%; 59% and 21%, respectively). Important information was obtained in terms of identifying key allergens in the crustacean-allergic population and the IgE epitopes of the four proteins presumptively involved in the allergic reactions. Seven epitopes were identified in tropomyosin (which are identical to those previously reported by our group), five in MLC, three in SCP, and six in AK. This study, however, included mostly non-challenged patients, which limits its value because of issues such as cross-reactivity among arthropod allergens.

Regarding mollusks, tropomyosin has been confirmed as an important allergen in cephalopods, gastropods, and bivalves, including snail (Tur c 1) [14], oyster (Cra g 1), scallop (Chl n 1), and mussel (Per v 1) [15]. However, a large number of molluscan allergens remain unidentified. Other proposed allergens include hemocyanin, myosin heavy chain, and amylase [16].

Cross-Reactivity of the Different Crustacean Allergens

In vitro IgE cross-reactivity among crustaceans, other arthropods, and mollusks is commonly reported. However, until recently, there had been only limited molecular characterization of these cross-reactive allergens. Tropomyosin traditionally has been accepted as the main cross-reactive molecule among crustaceans and also with mollusks [16]. In addition, important in vitro cross-reactivity exists between crustaceans and other invertebrates, such as dust mites (DM), cockroaches, and even nematodes [17]. Comparison of tropomyosin amino acid sequences from different crustacean species reveals very high homologies of up to 98%, whereas the amino acid sequence identity of shrimp tropomyosin with other arthropods such as DM and cockroaches is lower (80%), and still lower with mussels

and abalone (57% and 61%, respectively). The cross-reactivity among crustaceans, cockroaches, and DM seems to be based mostly on high-sequence identity of tropomyosin IgE-binding epitopes [18].

However, tropomyosin is not the only allergen involved in invertebrate cross-reactivity. AK has been described as a cross-reacting allergen among crustaceans, between crustaceans and insects [19], and possibly mollusks. Protein sequence analysis of Pen m 2 has shown the protein to be very similar to AK from moth (Plo i 1) [10, 19]. Recombinant moth AK reacted with serum from moth-allergic patients and inhibited the binding of allergic patients' IgE to an immunologically related, 40-kD allergen present in house DM, cockroach, king prawn, lobster, and mussel, indicating that AKs represent a new class of cross-reactive, invertebrate pan-allergens.

The newly identified shrimp MLC and SCP also appear to be involved in cross-reactivity. Interestingly, the amino acid sequence of MLC is 66% similar and 51% identical to cockroach Bla g 8, the allergenic MLC of *Blatella germanica* [11]. Sequence similarity between MLCs can be implicated for in vitro and possibly clinical cross-reactivity among shrimp and cockroach, and also possibly with DM. In contrast, sequence identity with other invertebrate MLCs, such as *Schistosoma* spp (identity 13%) and *Aedes* spp (17% identity), was low. With regard to SCP, the amino acid composition and physicochemical characteristics of different SCPs suggest that they are not conserved proteins. Because the biological function of SCP may be carried out without interacting with other proteins, there is little need to conserve surface amino acid residues. Sequence identity between shrimp and scallop SCP, for instance, is only 14%, and is also low with *Drosophila* spp (18%–52%). This is consistent with the lack of in vitro cross-reactivity seen by immunoblot with cockroach, DM, and mollusk SCPs in our study [12]. In contrast, high sequence identity with crawfish SCP (81%–82%) helps explain cross-reactivity detected among crustacean SCPs. This has been confirmed in immunoblot inhibition assays, in which lobster and crab extracts were able to inhibit the IgE reactivity to recombinant shrimp SCP.

In summary, while sensitization to tropomyosin has been implicated in cross-reactivity among crustaceans, mollusks, and other arthropods, AK and MLC may be cross-reactive among arthropods. In contrast, sensitization to SCP appears to be specific to crustacean allergy.

Issues with Cross-reactivity

It is well-described that crustaceans are highly cross-reactive among themselves, with mollusks, and with other invertebrates. Because of this extensive cross-reactivity, avoidance of all shellfish is frequently recommended for allergic individuals. This was challenged in a recent study [20•], which identified many participants who were mono-sensitized to individual shrimp species but not to others. This justifies, at least in this population, performing DBPCFCs to different crustaceans to identify the implicated species in order to allow the intake of other species that are shown to be safe. However, the real in vivo extent of the in vitro cross-reactivity among crustaceans has not been studied yet by performing DBPCFCs to different crustaceans. Thus, for most populations, a diagnosis of shellfish allergy still means avoiding all crustacean species.

With regard to mollusks, although the in vitro cross-reactivity appears to be important, the frequency of clinical reactivity to crustaceans and mollusks is reported to be low. Interestingly, only 14% of the shellfish-allergic individuals reported reactions to both crustaceans and mollusks in the questionnaire-based study by Sicherer et al. [1]. This low clinical cross-reactivity may be related to different epitopes in shrimp and mollusk tropomyosins.

In addition, there is also important in vitro cross-reactivity among arthropods. The question is, are the structural and immunochemical similarities of tropomyosins and other shrimp allergens in different invertebrate species (particularly mollusks, insects, and arachnids) of clinical significance? The question was raised by some studies that suggested that increased exposure of some patients to mite antigen through DM immunotherapy may result in sensitization to cross-reacting tropomyosins that did not exist before therapy [21, 22]. These studies raise some concern about the induction of food allergy through cross-reacting allergens in immunotherapy extracts. However, a systematic follow-up of 134 patients who underwent DM sublingual immunotherapy (SLIT) failed to document neosensitization to tropomyosin in any case [23]. These differences in responses may be due to varying amounts of tropomyosin present in the immunotherapy preparations. However, although the in vitro cross-reactivity is high, the risk of immunotherapy resulting in development of new sensitizations appears to be very low.

The problem of cross-reactivities among invertebrates may be especially relevant in terms of correct diagnosis of shellfish allergy in arthropod-allergic individuals (DM, cockroach), and also to determine the clinically relevant foods (crustaceans and/or mollusks). The relationship of molecular cross-reactivity to clinical reactivity has not been adequately defined to date. Although some studies have looked at rate of co-sensitization to DM, cockroach, and shrimp (based on serum IgE or skin prick test [SPT]), clinical cross-reactivity cannot be confirmed due to possible co-sensitization to different food and environmental allergens in atopic individuals. In this sense, identification of sensitization to particular shrimp allergens such as SCP, which are

more crustacean specific, may provide some help in making the correct diagnosis. Future research on the molecular structure of the cross-reacting shellfish allergens, with a focus on the immunologic and particularly clinical cross-reactivity, will improve diagnosis and management of shellfish allergy.

Natural History of Shellfish Allergy

Shellfish allergy traditionally has been seen as a long-lasting disease that typically persists into adulthood. Once patients are diagnosed with shellfish allergy, they typically avoid all shellfish for life. However, the natural history of shellfish allergy, which commonly begins in adult life, has not been systematically assessed. In the only study in which this was analyzed in the United States, 11 individuals with a clinical history of shrimp allergy were observed over 24 months; seven had positive food challenges, and all had stable IgE levels to shrimp during the study [24].

In recent work evaluating IgE binding to specific epitopes in the main four shrimp allergens, for diagnostic and prognostic purposes, we were able to show that sensitization to shrimp proteins is greater in children and appears to be lower in adults [13•]. Children with shrimp allergy had more intense binding to all shrimp proteins and bound more diverse epitopes compared with adults, suggesting a decrease in IgE reactivity with age and possible waning of the allergy. Authors also considered whether differences in allergen and epitope recognition in children and adults may be secondary to patient selection bias, resulting in higher shrimp-specific IgE in children than adults. However, comparison of peptide recognition in children and adults with similarly high shrimp-specific IgE levels (>100 kUA/L) showed greater binding in children. This study had the limitation that it was not a natural history study (ie, observing participants prospectively since childhood), and the patients were not challenged. Therefore, we cannot be certain whether these differences in allergen and epitope recognition are due to sensitization through distinct routes in children and adults (skin vs oral or respiratory) or stronger IgE responses when sensitized in childhood, or whether shrimp IgE really decreases over time. The possibility that shellfish allergy may wane over time needs to be confirmed in prospective studies using DBPCFC patients.

Diagnosis

As with other food allergies, diagnosis of shellfish allergy is based on clinical history and aided by skin testing and serum IgE determinations. However, the DBPCFC is the gold standard for diagnosis of food allergy. More recent experimental methodologies include the use of peptide and recombinant protein microarrays to diagnose food allergy and to identify individuals who are likely to have persistent disease. Recombinant allergens have been used to define the important allergens for a wide range of allergies, allowing the development of a component-based diagnosis for particular foods or environmental allergens. Many of these recombinant allergens, such as tropomyosin, have been shown to have similar properties as their native counterparts [25]. In addition, they have allowed the development of new types of immunotherapy, some of which have shown efficacy in human trials. With regard to shellfish, important allergens have been cloned and characterized, and their IgE epitopes identified [13•]. As our knowledge of shellfish allergen improves, we will be able to develop more accurate methods, incorporating the recombinant allergen tropomyosin, AK, MLC, and SCP in a component-based diagnosis of shellfish allergy. In addition, IgE epitope mapping of the main shellfish allergens will help identify sequential epitopes associated with clinical severity and persistent food allergy.

Boiled Extracts are Better Than Raw?

It is known that cooking may affect the allergenicity of foods such as peanut or shellfish. It may destroy certain epitopes in an allergen or may generate or expose new ones, probably as a result of changes in protein folding. Because most shellfish are consumed boiled, characterization of raw and boiled seafood extracts is important to select the best allergen extracts for standardization, diagnosis, and treatment of seafood-allergic patients. Carnes et al. [26] evaluated the in vivo and in vitro diagnostic yield of using raw or cooked extracts from shrimp and lobster. More patients were identified using boiled extracts of shrimp and American and spiny lobsters than with raw extracts. The wheal sizes of the skin test reactions and specific IgE levels determined by ELISA were also significantly greater using boiled extracts. The authors concluded that the use of boiled extracts seems to be more effective in diagnosing shellfish allergy. In an additional study, the thermal stability and IgE binding of raw and boiled shellfish extracts and tropomyosin were evaluated [27]. The soluble protein content as determined by ELISA and immunoblotting decreased, and the higher molecular weight proteins increased in the extracts from boiled versus raw shrimp. ELISA inhibition of raw shrimp with raw shrimp as inhibitor was higher than inhibition with boiled shrimp. However, no inhibitions were shown with boiled shrimp in the solid phase, and the IgE-binding capacities of raw and boiled extracts were not directly compared. Furthermore, Dot blot assay demonstrated higher IgE binding to purified tropomyosin from boiled shrimp than from raw shrimp. The authors concluded that boiling may decrease the allergenicity of shrimp, but

tropomyosin from boiled shrimp may be a more effective antigen in diagnosing shrimp allergy. However, the decrease in allergenicity of shrimp by boiling is not clearly supported by the data presented in this study.

Double-Blind, Placebo-Controlled Oral Food Challenge

The DBPCFC is the gold standard for diagnosis of food allergy, however, a single-blind or an open food challenge may be considered diagnostic under certain circumstances [28]. When DBPCFCs are used, several studies have shown that only about one third of the suspected foods are found to be truly allergic [28]. The presence of extensive cross-reactivity among crustaceans, mollusks, and other invertebrates emphasizes the need for DBPCFC for accurate diagnosis of shellfish allergy. However, the yield of positive DBPCFC for crustacean allergy varies greatly among different studies. In fact, Daul et al. [29] reported that 30% of their shrimp-allergic study participants had a positive challenge to shrimp. Also, a more recent report found that up to 50% of individuals with a history of shrimp allergy, positive SPT, or shrimp-specific serum IgE tolerated an oral challenge to shrimp [30]. In contrast to the previous works, Jirapongsananuruk et el. [20•] found up to 88% positive challenges. They studied 68 patients with history of shrimp allergy and positive SPT to shrimp. Seventeen percent were reactive in challenge to only Pm, 23% to *Macrobrachium rosenbergii* (Mr), and 47% to both. Interestingly, only 12% of the challenges were negative. However, all the patients in this study were children (which was in contrast to previous studies, which focused on mostly adults), demonstrating an increased yield of positive challenges in children. This is discussed later, as it may suggest a possible decrease in reactivity to shrimp proteins with age. This study shows for the first time using DBPCFC that sensitization to individual shrimp species may exist and is frequent in Thailand.

As a means to avoid DBPCFC due to increased risk of reactions during the challenges, attempts have been made to determine whether reactivity by SPT, specific IgE to shrimp, or certain allergens or their epitopes correlates well with clinical reactivity. Yang et al. [31•] recently studied the clinical implication of the detection of specific IgE antibodies to shrimp tropomyosin. Sensitization to tropomyosin was found to have greater diagnostic efficiency compared with measurement of specific IgE to shrimp and SPT (88.5%, 74.2%, and 65.7%, respectively) [31•]. However, the diagnostic value of the other three shrimp allergens and its relationship to the clinical symptoms have not been well-established thus far. Also, Jirapongsananuruk et al. [20•] calculated the predictive probability of mean wheal diameter (MWD) induced by Pm and Mr SPT/prick-to-prick testing/commercial SPT to determine the outcome of shrimp challenges, using logistic regression to establish the reasonable cutoff level. In the Pm allergy group, Pm SPT with an MWD of 30 mm provided 80% predictive probability for positive challenges. Pm prick-to-prick testing and commercial SPT with an MWD of 22.5 and 20 mm, respectively, provided 95% predictive probability. In the Mr allergy group, Mr SPT with an MWD of 30 mm provided 95% predictive probability.

Treatment of Shellfish Allergy

Despite the high prevalence of shellfish allergy, few options are available for treatment, and avoidance of the offending food is the only therapy recommended. However, the frequency and severity of reactions after accidental exposure to shellfish make necessary the development of improved diagnostic and therapeutic options for shellfish allergy.

Non–allergen-specific therapeutic approaches for food allergy have shown some promising results, but uniform response to the therapy is either lacking (eg, anti-IgE) [32], or the long-term effects still need to be determined (eg, Chinese herbal medicine food allergy herbal formula [FAHF]-2) [33, 34]. Most of the studies thus far have been conducted for treatment of peanut, milk, or egg allergy, but it may be possible to apply them to other foods. Anti-IgE improves symptoms of asthma and allergic rhinitis and provides protection against peanut-induced anaphylaxis in 75% of treated patients (highest dose group); however, the consequences of long-term elimination of IgE are unknown. The Chinese herbs FAHF-2 produce a downregulation of T-helper type 2 cytokines (interleukin [IL]-4, IL-5, IL-13) and decreased allergen-specific IgE levels and T-cell proliferation to peanut, and protect mice from peanut-induced anaphylaxis for prolonged periods of time. Current studies focus on establishing optimal dosing in human phase 1 and phase 2 trials [35].

Another non–allergen-specific approach includes the use of probiotic bacteria. Dietary lactic acid bacteria are regarded as safe and are used extensively in fermented food products. They modulate the immune system via their effect on different pathways, including direct actions on antigen-presenting cells, regulatory T cells, and effector B and T cells, and promote T-helper type 1 differentiation. They also stimulate systemic and mucosal immune responses, eliciting the production of secretory IgA. Clinical trials of probiotics have focused on the prevention and treatment of atopic dermatitis, which includes a large subset of children with food allergy. Also, lactic acid bacteria have been tested in murine models to evaluate their protective effect on the development and treatment of food and environmental allergy [36, 37]. In a murine model of shrimp-induced anaphylaxis, oral administration of a pro-

biotic mixture significantly reduced symptom scores, serum shrimp-specific IgE, and histamine release in the stool after a shrimp tropomyosin oral challenge [38]. In the jejunum, IL-4, IL-5, and IL-13 expression was significantly reduced, whereas forkhead box P3 and IL-27 mRNA expression and IL-10, transforming growth factor-β, and interferon-γ tissue content were upregulated. In addition, other possible approaches, such as use of Toll-like receptor 9 agonists [39], are in preclinical stages.

Among allergen-specific approaches, subcutaneous immunotherapy has not been recommended due to the high risk of severe reactions during the immunotherapy protocol [40]. Recently, oral immunotherapy (OIT) [41, 42] and SLIT [43] have received the most attention. Studies with egg, milk, and peanut show that OIT desensitizes most patients. However, there is no evidence that OIT yields long-term tolerance. Although many patients tolerate increased amounts of allergen after OIT or SLIT than they did at baseline challenge, the risk of anaphylactic reactions is still present during the desensitization, and many questions and concerns remain regarding whether these regimens can induce permanent tolerance or only desensitization during dosing.

Another allergen-specific immunotherapy approach includes the use of engineered recombinant food proteins. The importance of sequential epitopes in food allergy has been established. Sensitization to sequential epitopes has been associated with persistent and more severe reactions to peanut [44], milk [45], and egg [46]. Identifying the sequential IgE-binding epitopes of shellfish allergens and the critical amino acids for IgE binding are important because they provide the information to alter the complementary DNA nucleotide sequences for the production of recombinant allergen variants with lower anaphylactic potential while keeping their T-cell epitopes intact for the induction of tolerance. This approach has resulted in the development of recombinant mutant variants of different allergens. However, limited information is available regarding recombinant food allergens for immunotherapy. In the first proof-of-concept, in vivo studies to date using a mutant hypoallergenic vaccine in a food allergy model, mice were treated with heat-killed *Escherichia coli* or *Listeria monocytogenes* producing mutated Ara h 1, 2, and 3 [47, 48]. The heat-killed *E. coli* vaccine is currently in clinical trials. However, although it has demonstrated protection from anaphylaxis, the heat-killed *E. coli* vaccine can only be administered rectally. In addition, the risk of reactivation of vectors such as *Listeria* spp in humans is not acceptable. A similar approach has resulted in the development of a mutant parvalbumin for immunotherapy for fish-allergic individuals [49].

With regard to shellfish, our group has developed a mutant tropomyosin with decreased allergenic potential for treatment of shellfish allergy [50]. Using one or two amino acid substitutions per epitope, a hypoallergenic tropomyosin mutant was designed. The Pen a 1 mutant and wild-type Pen a 1 were compared for their capacity to induce mediator release from RBL-30/25 cells. Sensitized cells with sera from shrimp-allergic patients showed higher mediator release with the wild-type Pen a 1 than with the mutant, which required 10- to 40-fold higher concentrations to induce 50% of maximal release than the wild type. However, this Pen a 1 mutant still showed some allergenic potency at high concentrations. Although promising, this mutant may need additional amino acid substitutions to further decrease its IgE-binding capacity. In addition, any immunotherapy approach to shellfish allergy will need to take into consideration additional shrimp allergens, including MLC and SCP, because they seem to be important in certain populations.

Conclusions

In conclusion, shellfish is a lifelong disorder affecting a significant percentage of the population and causing life-threatening complications. Recent research has better characterized the allergens responsible for such reactions in adult and pediatric populations, suggesting that stronger sensitization occurs in children. However, issues of cross-reactivity limit the accuracy of current diagnostic tests, and the DBPCFC is still the gold standard for diagnosis. As our knowledge of shellfish allergen improves, we will be able to develop more accurate methods of diagnosing shellfish allergy using a component-based system. In addition, recent advances in different therapeutic approaches for food allergy are yielding promising results. In particular, development of a vaccine composed of hypoallergenic shrimp proteins appears to be a good candidate for treatment of shellfish-allergic individuals in the near future.

Acknowledgments Dr. Ayuso is supported by the Food Allergy Initiative and by the Mount Sinai School of Medicine. She would like to thank Dr. Peter Gontzes for editorial support.

Disclosure No potential conflict of interest relevant to this article was reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the united states determined by a random telephone survey. J Allergy Clin Immunol. 2004;114(1):159–65.

2. Castillo R, Delgado J, Quiralte J, et al. Food hypersensitivity among adult patients: epidemiological and clinical aspects. Allergol Immunopathol Madr. 1996;24(3):93–7.
3. Ben-Shoshan M, Harrington DW, Soller L, et al. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in canada. J Allergy Clin Immunol. 2010;125(6):1327–35.
4. Shek LP, Soderstrom L, Ahlstedt S, et al. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. J Allergy Clin Immunol. 2004;114(2):387–91.
5. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol. 2010;126(4):798–806.
6. Clark S, Bock SA, Gaeta TJ, et al. Multicenter study of emergency department visits for food allergies. J Allergy Clin Immunol. 2004;113(2):347–52.
7. Ross MP, Ferguson M, Street D, et al. Analysis of food-allergic and anaphylactic events in the national electronic injury surveillance system. J Allergy Clin Immunol. 2008;121(1):166–71.
8. Banerji A, Rudders SA, Corel B, et al. Predictors of hospital admission for food-related allergic reactions that present to the emergency department. Ann Allergy Asthma Immunol. 2011;106(1):42–8.
9. Daul CB, Slattery M, Reese G, Lehrer SB. Identification of the major brown shrimp (Penaeus aztecus) allergen as the muscle protein tropomyosin. Int Arch Allergy Immunol. 1994;105(1):49–55.
10. Yu CJ, Lin YF, Chiang BL, et al. Proteomics and immunological analysis of a novel shrimp allergen, Pen m 2. J Immunol. 2003;170(1):445–53.
11. Ayuso R, Grishina G, Bardina L, et al. Myosin light chain is a novel shrimp allergen, Lit v 3. J Allergy Clin Immunol. 2008;122:795–802.
12. Ayuso R, Grishina G, Ibanez MD, et al. Sarcoplasmic calcium-binding protein is an EF-hand-type protein identified as a new shrimp allergen. J Allergy Clin Immunol. 2009;124(1):114–20.
13. • Ayuso R, Sanchez-Garcia S, Lin J, et al. Greater epitope recognition of shrimp allergens by children than by adults suggests that shrimp sensitization decreases with age. J Allergy Clin Immunol. 2010;125(6):1286–93. *This study showed stronger sensitization to shrimp allergens in children than in adults, suggesting a possible decrease in sensitization with age.*.
14. Ishikawa M, Ishida M, Shimakura K, et al. Purification and IgE-binding epitopes of a major allergen in the gastropod turbo cornutus. Biosci Biotechnol Biochem. 1998;62(7):1337–43.
15. Chu KH, Wong SH, Leung PS. Tropomyosin is the major mollusk allergen: reverse transcriptase polymerase chain reaction, expression and IgE reactivity. Mar Biotechnol NY. 2000;2(5):499–509.
16. Taylor SL. Molluscan shellfish allergy. Adv Food Nutr Res. 2008;54:139–77.
17. Reese G, Ayuso R, Lehrer SB. Tropomyosin: an invertebrate pan-allergen. Int Arch Allergy Immunol. 1999;119(4):247–58.
18. Ayuso R, Reese G, Leong-Kee S, et al. Molecular basis of arthropod cross-reactivity: IgE-binding cross-reactive epitopes of shrimp, house dust mite and cockroach tropomyosins. Int Arch Allergy Immunol. 2002;129(1):38–48.
19. Binder M, Mahler V, Hayek B, et al. Molecular and immunological characterization of arginine kinase from the indian meal moth, Plodia interpunctella, a novel cross-reactive invertebrate pan-allergen. J Immunol. 2001;167(9):5470–7.
20. • Jirapongsananuruk O, Sripramong C, Pacharn P, et al. Specific allergy to Penaeus monodon (seawater shrimp) or Macrobrachium rosenbergii (freshwater shrimp) in shrimp-allergic children. Clin Exp Allergy. 2008;38(6):1038–47. *This was the first study to show, using DBPCFCs, that sensitization to particular shrimp species while tolerating others can occur and is common in Thailand. This has implications for avoidance recommendations in shellfish-allergic individuals.*.
21. van Ree R, Antonicelli L, Akkerdaas JH, et al. Possible induction of food allergy during mite immunotherapy. Allergy. 1996;51(2):108–13.
22. Pajno GB, La Grutta S, Barberio G, et al. Harmful effect of immunotherapy in children with combined snail and mite allergy. J Allergy Clin Immunol. 2002;109(4):627–9.
23. Asero R. Lack of de novo sensitization to tropomyosin in a group of mite-allergic patients treated by house dust mite-specific immunotherapy. Int Arch Allergy Immunol. 2005;137(1):62–5.
24. Daul CB, Morgan JE, Lehrer SB. The natural history of shrimp hypersensitivity. J Allergy Clin Immunol. 1990;86(1):88–93.
25. Reese G, Schicktanz S, Lauer I, et al. Structural, immunological and functional properties of natural recombinant Pen a 1, the major allergen of brown shrimp, Penaeus aztecus. Clin Exp Allergy. 2006;36(4):517–24.
26. Carnes J, Ferrer A, Huertas AJ, et al. The use of raw or boiled crustacean extracts for the diagnosis of seafood allergic individuals. Ann Allergy Asthma Immunol. 2007;98(4):349–54.
27. Liu GM, Cheng H, Nesbit JB, et al. Effects of boiling on the IgE-binding properties of tropomyosin of shrimp (Litopenaeus vannamei). J Food Sci. 2010;75(1):T1–5.
28. Boyce JA, Assa'a A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the united states: summary of the NIAID-sponsored expert panel report. Nutrition. 2011;27(2):253–67.
29. Daul CB, Morgan JE, Hughes J, et al. Provocation-challenge studies in shrimp-sensitive individuals. J Allergy Clin Immunol. 1988;81(6):1180–6.
30. Sanchez-Garcia S, Gamez C, Lopez E, et al. Allergy to shrimp: a double blind, placebo-controlled, food challenge study and allergens implicated in Spain. J Allergy Clin Immunol. 2009;123(2):S23.
31. • Yang AC, Arruda LK, Santos AB, et al. Measurement of IgE antibodies to shrimp tropomyosin is superior to skin prick testing with commercial extract and measurement of IgE to shrimp for predicting clinically relevant allergic reactions after shrimp ingestion. J Allergy Clin Immunol. 2010;125(4):872–8. *This study showed that use of measurements of IgE to shrimp tropomyosin adds value to the diagnosis of shrimp allergy. This is important for the diagnosis of shellfish allergy in the arthropod-allergic population with a positive SPT to shrimp.*.
32. Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348(11):986–93.
33. Srivastava KD, Kattan JD, Zou ZM, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. J Allergy Clin Immunol. 2005;115(1):171–8.
34. Srivastava KD, Qu C, Zhang T, et al. Food allergy herbal formula-2 silences peanut-induced anaphylaxis for a prolonged posttreatment period via IFN-gamma-producing CD8+ T cells. J Allergy Clin Immunol. 2009;123(2):443–51.
35. Wang J, Patil SP, Yang N, et al. Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study. Ann Allergy Asthma Immunol. 2010;105(1):75–84.
36. Hisbergues M, Magi M, Rigaux P, et al. In vivo and in vitro immunomodulation of Der p 1 allergen-specific response by Lactobacillus plantarum bacteria. Clin Exp Allergy. 2007;37(9):1286–95.
37. Hougee S, Vriesema AJ, Wijering SC, et al. Oral treatment with probiotics reduces allergic symptoms in ovalbumin-sensitized

mice: a bacterial strain comparative study. Int Arch Allergy Immunol. 2009;151(2):107–17.
38. Schiavi E, Barletta B, Butteroni C, et al. Oral therapeutic administration of a probiotic mixture suppresses established Th2 responses and systemic anaphylaxis in a murine model of food allergy. Allergy. 2010 Nov 8 (Epub ahead of print).
39. Zhu FG, Kandimalla ER, Yu D, et al. Oral administration of a synthetic agonist of Toll-like receptor 9 potently modulates peanut-induced allergy in mice. J Allergy Clin Immunol. 2007;120(3):631–7.
40. Nelson HS, Lahr J, Rule R, et al. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol. 1997;99(6 Pt 1):744–51.
41. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124:292–300.
42. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122(6):1154–60.
43. Enrique E, Pineda F, Malek T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116(5):1073–9.
44. Flinterman AE, Knol EF, Lencer DA, et al. Peanut epitopes for IgE and IgG4 in peanut-sensitized children in relation to severity of peanut allergy. J Allergy Clin Immunol. 2008;121(3):737–43.
45. Jarvinen KM, Beyer K, Vila L, et al. B-cell epitopes as a screening instrument for persistent cow's milk allergy. J Allergy Clin Immunol. 2002;110(2):293–7.
46. Jarvinen KM, Beyer K, Vila L, et al. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. Allergy. 2007;62(7):758–65.
47. Li XM, Srivastava K, Grishin A, et al. Persistent protective effect of heat-killed Escherichia coli producing "engineered," recombinant peanut proteins in a murine model of peanut allergy. J Allergy Clin Immunol. 2003;112(1):159–67.
48. Li XM, Srivastava K, Huleatt JW, et al. Engineered recombinant peanut protein and heat-killed Listeria monocytogenes coadministration protects against peanut-induced anaphylaxis in a murine model. J Immunol. 2003;170(6):3289–95.
49. Swoboda I, Bugajska-Schretter A, Linhart B, et al. A recombinant hypoallergenic parvalbumin mutant for immunotherapy of IgE-mediated fish allergy. J Immunol. 2007;178(10):6290–6.
50. Reese G, Viebranz J, Leong-Kee SM, et al. Reduced allergenic potency of VR9-1, a mutant of the major shrimp allergen Pen a 1 (tropomyosin). J Immunol. 2005;175(12):8354–64.